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BRIEF REPORT

Real-World Experience With Maribavir for Treatment of Cytomegalovirus Infection in High-Risk Solid Organ Transplant Recipients

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We evaluated use of maribavir (MBV) for treatment of 15 episodes of refractory/resistant cytomegalovirus infection in 13 solid organ transplant recipients. Treatment failure due to treatment-emergent MBV resistance or early virological recurrence after MBV discontinuation occurred in 7 (47%) episodes. Sustained viral clearance was achieved in 6 (40%) episodes.

Keywords. cytomegalovirus; maribavir; solid organ transplantation; antiviral drug resistance; antiviral therapy.

Cytomegalovirus (CMV) infection remains a significant cause of morbidity and mortality among solid organ transplant (SOT) recipients [1]. CMV treatment is often complicated by drug toxicities, intolerances, and variable treatment responses. In addition, fluctuation in renal function after SOT is common and may lead to underdosing of CMV antiviral prophylaxis. Suboptimal antiviral prophylaxis dosing in the context of immunosuppression facilitates the development of breakthrough CMV infection, refractory CMV infection, and antiviral resistance [2].

Maribavir (MBV), a novel, oral CMV UL97 protein kinase inhibitor, was approved by the US Food and Drug Administration in November 2021 for the management of refractory/resistant CMV infection. In clinical trials among hematopoietic cell transplant and SOT recipients for treatment of refractory/resistant CMV infection, up to 44% of participants receiving MBV did not achieve the primary endpoint of viral clearance, and up to 35% of initial responders developed recurrent CMV infection [3, 4]. Similarly, in clinical trials comparing MBV to valganciclovir for preemptive treatment of CMV infection, higher rates of CMV recurrence on therapy were observed in MBV arms, and up to 22% of initial responders developed recurrent viremia after stopping MBV [5, 6]. Rates of treatment-emergent resistance while on MBV ranged from 8.8% to 10.8% in these studies [3, 6]. Postmarketing surveillance data with MBV remain limited [7, 8]. Although MBV is a promising new treatment, its optimal application in the broader context of CMV management is not yet fully elucidated. We present our experience using MBV for treatment of resistant/refractory CMV infection in SOT recipients at a large-volume academic transplant center.

METHODS

We conducted a single-center, retrospective study of all SOT recipients treated with MBV for refractory/resistant CMV infection from June 2020 to October 2022 at Duke University Hospital (DUH). This study was approved by the Duke University Health System Institutional Review Board. Patient demographics, transplant history, immunosuppressive therapy (IST), CMV treatment details, and treatment outcomes were abstracted from the electronic health records. Creatinine clearance was estimated by the Cockcroft-Gault equation; creatinine clearance <60 mL/minute was considered impaired renal function. Quantitative plasma CMV polymerase chain reaction (PCR) testing was performed at DUH utilizing the COBAS AmpliPrep/COBAS TaqMan CMV test (Roche, Indianapolis, Indiana), or collected locally and sent to reference laboratories, depending on time posttransplantation and patient's distance from DUH. CMV drug resistance testing, including for MBV resistance, was performed at reference laboratories (Eurofins Viracor and Mayo Clinic Laboratories). All CMV-seronegative recipients of organs from CMV-seropositive donors (D^+/R^-) received primary prophylaxis following transplant per DUH organ-specific protocols as previously published (lifelong prophylaxis for D^+/R^- lung recipients; 6 months of prophylaxis for other D^+/R^- organ groups) [9]. Accepted clinical trial definitions for CMV infection and disease in transplant recipients were used [10]. Resistant and refractory CMV infection and disease were defined as previously outlined by Chemaly et al [11]. Each discrete MBV treatment episode was assessed as a continuous period of MBV therapy (with or without adjunctive treatments such as CMV-specific immunoglobulin) until discontinued by the treating provider. Use of secondary

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prophylaxis following treatment was also at the discretion of the treating provider. A successful MBV treatment episode was defined as achieving viral clearance (2 CMV PCR assay values below the lower limit of quantification [LLOQ], eg, <137 IU/mL, on consecutive evaluations separated by at least 1 week), with sustained viral clearance (no increase in CMV viral load) for at least 4 weeks after MBV completion. MBV treatment failure was defined as the inability to achieve CMV viral clearance or rising CMV viral load while receiving MBV, with or without documented genotypic MBV resistance. Rising CMV viral load was delineated as plasma CMV DNA concentration greater than the LLOQ in 2 consecutive plasma samples, as measured by the same assay, after achieving viral clearance. Development of new end-organ CMV disease with or without concurrent DNAemia was also considered treatment failure. CMV recurrence was defined as either rising CMV viral load or clinical signs of CMV disease necessitating alternative anti-CMV therapy within 4 weeks of MBV discontinuation. Patients who did not achieve viral clearance by the time of MBV discontinuation due to inability to obtain additional MBV, but had downtrending CMV DNAemia, were considered partial responders. Clinical follow-up data were analyzed through 12 months after MBV initiation. Data were summarized using descriptive statistics.

RESULTS

Thirteen SOT recipients (4 lung, 3 heart, 2 liver, 2 kidney and 2 multiorgan) received MBV for refractory/resistant CMV across 15 discrete treatment episodes (Table 1). Two patients received 2 MBV treatment courses each. The 13 patients had a median age of 57 (interquartile range [IQR], 53–61) years at the time of MBV initiation. The median time from transplant to CMV infection was 165 (IQR, 92–216) days, and the median time from transplant to MBV initiation was 282 (IQR, 171–369) days (Supplementary Table 1). All patients were CMV D^+/R^-, and the majority (85% [11/13]) were receiving CMV primary prophylaxis at the time of initial CMV infection diagnosis, for a median of 115 (IQR, 61–166) days. At the time of MBV treatment initiation, 11 (73%) cases had asymptomatic CMV DNAemia, and 4 (27%) had probable or proven end-organ disease (upper and/or lower gastrointestinal disease and pneumonitis). The majority of MBV treatment episodes were for refractory and resistant CMV infection with documented UL97 and/or UL54 genotypic resistance (11 episodes, 73%). Three episodes (20%) were refractory infections without documented genotypic resistance (no detected resistance in 2 episodes and no genotyping performed in 1 episode). The remaining episode was the second of 2 MBV courses given to a patient with recurrent CMV infection immediately after completing MBV treatment for refractory/resistant infection. CMV-specific immunoglobulin was used as adjunctive anti-CMV therapy along with MBV treatment in 4 episodes (patients B, J, and K).

The median duration of MBV across all treatment episodes was 61 (IQR, 59–71) days. Sustained CMV viral clearance was achieved with MBV in 6 (40%) episodes while treatment failure due to treatment-emergent MBV resistance was observed in 4 (27%) episodes (identified genotypic mutations included C480F [n = 2], T409M [n = 1], F342Y [n = 1]) [12, 13]). There were 3 (20%) episodes of successful treatment followed by CMV recurrence within 4 weeks of MBV discontinuation (33% CMV recurrence rate among those with initial successful treatment) as well as 2 (13%) episodes of partial response with discontinuation of MBV prior to achieving undetectable CMV PCR due to inability to obtain additional MBV. Of the 3 CMV recurrence cases, 1 patient was successfully retreated with a second course of MBV (patient A). The other 2 cases initially received alternative therapy. One patient was successfully treated with valganciclovir (patient G). The other patient received ganciclovir and valganciclovir before developing a new UL97 mutation and subsequently failing a second MBV course with emergence of MBV resistance (patient J). In both partial responder instances, a decrease in CMV DNAemia was observed, but viral clearance was not achieved despite 8 weeks of MBV treatment.

In aggregate, 7 (47%) MBV treatment episodes resulted in treatment-emergent resistance or early virologic recurrence, necessitating the use of alternative anti-CMV therapies or the resumption of MBV. Notably, a higher median starting CMV viral load at the onset of MBV therapy was observed in the treatment failure or early recurrence group (n = 7) (41 001 [IQR, 31 750–48 144] IU/mL) compared to the group that achieved and maintained CMV clearance with MBV (n = 6) (1434 [IQR, 1145–3598] IU/mL). MBV was generally well-tolerated; dysgeusia was reported in 85% of patients, but no MBV discontinuations occurred due to adverse drug effects. In 11 episodes (73%), impaired renal function was present prior to MBV treatment, necessitating dose adjustments to prior CMV prophylaxis or treatment regimens. Creatinine clearance remained similar prior to and after MBV treatment in all outcome groups (overall cohort median creatinine clearance at MBV start was 40 [IQR, 34–52] mL/minute, and median creatinine clearance at MBV end was 42 [IQR, 34–56] mL/minute). At 12 months after MBV initiation, 1 of 13 (8%) patients had died due to causes unrelated to CMV infection. Six (46%) patients were maintained on alternative anti-CMV agents for secondary prophylaxis (letermovir in all instances), and 6 (46%) had ceased CMV antivirals.

DISCUSSION

We evaluated treatment outcomes in this real-world cohort of high-risk SOT recipients treated with MBV for refractory and/

Table 1. Baseline Characteristics and Outcomes of Solid Organ Transplant Recipients Who Received Maribavir for Refractory/Resistant Cytomegalovirus Infection

Patient ID	Age, y	Sex	Race	SOT Type	CMV Infection Classification[a]	Reason for Change to MBV	Genotypic Resistance	CMV VL at MBV Start, IU/mL	CMV VL at MBV End, IU/mL	MBV Duration for Episode, d	MBV Outcome	Time to Relapse, d	MBV Resistance	Outcome up to 1 y
Successful treatment with MBV														
A	57	M	B	Lung	DNAemia	Prior refractory w/ resistance	Not performed	840	0	105	Success	…	…	CMV ppx
B	53	F	W	Lung	DNAemia	Refractory w/resistance	UL54 C539R, S290R	3598	<200	56	Success	…	…	CMV ppx
C	72	M	W	Lung	Disease (probable pneumonitis)	Refractory w/resistance	UL97 A594V	1145	0	104	Success	…	…	CMV ppx
D	58	M	B	Heart	DNAemia	Refractory w/resistance	UL97 L595S	1434	0	124	Success	…	…	Off CMV therapies
E	54	M	W	Liver	DNAemia	Refractory	None	101 237	0	61	Success	…	…	Off CMV therapies
F	59	M	B	Liver	Disease (proven GI)	Refractory	Not performed	<200	0	59	Success	…	…	Off CMV therapies
Treatment failure or CMV recurrence within 4 wk of completing MBV														
G	45	M	B	Kidney-Pancreas	DNAemia	Refractory w/resistance	UL97 H520Q	3150	0	118	Relapse	27	Not performed	Off CMV therapies
H	57	F	B	Kidney	DNAemia	Refractory w/resistance	UL97 M460V	773	13 200	88	Failure	0	UL97 C480F	Off CMV therapies
I	23	F	B	Kidney-Liver	DNAemia	Refractory	None	1724	10 018	61	Failure	0	UL97 C480F	CMV ppx
A	57	M	B	Lung	DNAemia	Refractory w/resistance	UL97 C603W	54 288	<137	77	Relapse	13	Not performed	CMV ppx
J	41	M	B	Heart	DNAemia	Refractory w/resistance	UL54 T700A	10 200	1420[b]	60	Relapse	1	Not performed	CMV treatment
J	41	M	B	Heart	DNAemia	Refractory w/resistance	UL97 L595S	842	11 300	49	Failure	0	UL97 T409M	CMV ppx
K	61	M	W	Heart	Disease (proven GI)	Refractory w/resistance	UL97 C603W	187 506	40 600	52	Failure[c]	0	UL97 F342Y	CMV ppx
Partial response														
L	65	M	B	Kidney	DNAemia	Refractory w/resistance	UL97 L595S; UL54 A834P, V715M	254 000	939	72	Other	…	…	Off CMV therapies
M	76	M	W	Lung	Disease (probable pneumonitis)	Refractory w/resistance	UL97 L595F	13 884	391	59	Other	…	…	Deceased (unrelated to CMV)

Abbreviations: B, Black; CMV, cytomegalovirus; F, female; GI, gastrointestinal; M, male; MBV, maribavir; ppx, prophylaxis; SOT, solid organ transplant; VL, viral load; W, White.

[a]CMV infection classification at time of MBV start.

[b]CMV polymerase chain reaction (PCR) reached undetectable level while receiving MBV treatment but rose to 1420 IU/mL on the day MBV was discontinued, leading treatment episode to be categorized as successful treatment followed by recurrence.

[c]CMV PCR was down-trending on MBV but patient developed new vision changes and was diagnosed with CMV retinitis approximately 7 weeks into MBV therapy. Genotypic resistance testing revealed a UL97 F342Y mutation conferring MBV resistance.

or resistant CMV infection. MBV represents an important therapeutic advancement for the management of refractory/resistant CMV infection and is an attractive alternative to traditional antivirals due to its oral formulation and favorable safety profile. Our study corroborates the meaningful rate (31%) of CMV recurrence observed in a separate real-world cohort of SOT recipients treated with MBV [7]. We documented treatment failure due to the emergence of MBV resistance or virological recurrence in 47% of treatment episodes, similar to prior MBV clinical trial experience [3–6]. Patients who experienced treatment failure or recurrence had higher CMV viral loads than patients for whom MBV treatment was successful. Patients with CMV disease also experienced variable outcomes (2 successes, 1 failure/recurrence, 1 partial response), but small patient numbers limit the ability to draw meaningful conclusions from these observations. Renal dysfunction prior to and during MBV treatment was common in this cohort, but creatinine clearance remained similar before and after MBV treatment. Dysgeusia was almost universal, but was never severe enough to require MBV discontinuation.

Heterogeneity in the use of secondary prophylaxis and the duration of MBV treatment may confound the assessment of sustained clinical response after MBV treatment. Two of 7 patients who received secondary prophylaxis after successful treatment with MBV developed CMV recurrence, while 1 of 2 patients who did not receive secondary prophylaxis after MBV treatment experienced recurrent infection (Supplementary Table 1). Further investigations are needed to compare CMV recurrence rates after MBV treatment with and without secondary prophylaxis. In this study, MBV duration varied at the treating provider's discretion. Phase 3 clinical trials employed an 8-week treatment course, and the efficacy of shorter or longer durations remains unexplored. Some patients require extended treatment beyond 8 weeks, highlighting the need for further data to determine the ideal duration of MBV therapy for CMV infections. Other patients may achieve viral clearance before the 8-week mark, and earlier cessation of MBV, with or without secondary prophylaxis, may reduce apparent treatment failures.

This study has limitations. First, its retrospective, single-center design and small sample size limit the generalizability of findings. The duration of MBV treatment and decision to use CMV secondary prophylaxis after treatment was, in most instances, at the discretion of the treating provider. Additionally, CMV viral load monitoring was performed using different assays across multiple laboratories, leading to potential variability in comparisons. Furthermore, variations in IST (both maintenance IST as well as treatment for rejection) and heterogenous practices in IST reduction (Supplementary Table 1) may have influenced CMV infection outcomes. Due to the limited sample size and heterogeneity within our cohort, direct comparisons between patients who cleared the infection and those who experienced recurrence/nonresponse were challenging, and we could not identify differences based on IST. Last, there was no non-MBV comparator group.

While MBV represents a promising new therapy for difficult-to-treat CMV infections in transplant recipients, high rates of MBV treatment failure and CMV recurrence reflect the limitations of antivirals in patients with persistent immune deficits. MBV should be used cautiously and with vigilant monitoring for potential emergence of MBV resistance or recurrence. Further investigations are warranted to elucidate optimal treatment duration, viral load thresholds for initiating MBV, and the role of MBV in combination with other antivirals and interventions to enhance CMV-specific immunity.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. E. K. M. and B. N. conceptualized the idea for this report. All authors performed chart review and data collection. B. N. and E. K. M. prepared the original draft. C. R. W., S. A., M. C., M. R. H., J. A. M., R. A. M., J. L. S., and A. W. B. provided critical review, commentary, and revision of the draft. All authors reviewed the results and approved the final version of the manuscript.

Data availability. De-identified data supporting the findings of this study will be available after the approval of a data use proposal. Proposals may be submitted to eileen.maziarz@duke.edu.

Patient consent. The research conducted for this study was approved by the Duke University Institutional Review Board. Written patient consent was not required due to the retrospective nature of the study, and waivers of informed consent were granted.

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Potential conflicts of interest. All authors: No reported conflicts.

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